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REMARKS

Claims 1-13 and 16-33 are pending in the above application. Claims 25-33 are withdrawn as directed to a non-elected invention. Claims 1 and 25-33 are canceled herein without prejudice. Claims 2-13 are amended herein and rewritten in independent form for clarity to more particularly define the invention. The specification is amended herein to correct a citation to a non-patent reference, as requested by the Examiner. Support for these amendments is found in the language of the original claims, in particular in claim 1, and throughout the specification as set forth below. No new matter is added by these amendments and applicants respectfully request their entry and consideration. In light of these amendments and the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Specification

The Office Action states that the specification is objected to due to a typographical error in the citation of a reference by Stockmann et al. on page 11, line 24.

The specification is amended herein to correct the Stockmann et al. citation, pursuant to the Examiner's request. Therefore applicants respectfully request the withdrawal of this objection.

II. Claim objections

The Office Action states that claims 1-13 are objected to because independent claim 1 refers to an "active PAI-1/multimeric vitronectin complex," while the dependent claims refer to the "PAI-1/multimeric vitronectin complex." It is suggested that consistent terminology should be used throughout the claims.

Claim 1 is canceled herein without prejudice, rendering this objection with respect to that claim moot. Claims 2-13 are amended herein to recite an "active PAI-1/multimeric vitronectin

complex" throughout, further rendering this objection moot. Applicants therefore respectfully request its withdrawal.

III. Rejection under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 1-13 and 16-24 are rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement, specifically, for containing new matter. Namely, the Examiner has stated that support cannot be found in the specification for platelet releasates, platelet plasma, or combinations of the recited fluids.

Claims 1-13 and 16-24 are amended herein to recite that the biological fluid is whole blood, plasma or serum; thereby rendering this rejection moot and Applicants therefore respectfully request its withdrawal.

IV. Rejection under 35 U.S.C. § 112, second paragraph

The Office Action states that claims 1-13 and 16-24 are rejected under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action states that "said amount" as recited in claim 1 (now recited in claims 2-13) is ambiguous.

Claim 1 is canceled herein without prejudice, thereby mooting this rejection as it pertains to that claim. Applicants have amended the term "said amount" as it is now recited in claims 2-13, to the term "the amount of active PAI-1 in the biological fluid." A key aspect of the present invention is that the amount of active PAI-1 in the biological fluid can be determined utilizing, or correlated to, the amount of the active PAI-1/multimeric vitronectin complex in the sample. Applicants respectfully submit that the claims as presented herein are clear and unambiguous to a person skilled in the art, thereby overcoming this rejection and applicants respectfully request its withdrawal.

V. Rejection under 35 U.S.C. § 102(b)

The Office Action states that claim 1 is rejected under 35 USC § 102(b) as allegedly being anticipated by Sieffert et al.

Claim 1 is canceled herein without prejudice, rendering this rejection moot and Applicants respectfully request its withdrawal.

VI. Rejection under 35 U.S.C. § 103

A. The Office Action states that claims 1-11 and 23-24 are rejected under 35 USC § 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al. Specifically, the Office Action states that:

- Hamsten teaches that measurement of PAI-1 activity was known in the art to be used for predicting myocardial infarction. However, the Office Action confirms that Hamsten does not teach measuring PAI-1 activity by measuring active PAI-1 in complex with multimeric vitronectin.
- Preissner et al. teaches a method of measuring the amount of PAI-1 in complex with vitronectin in biological fluid samples including platelet releasates and platelet lysates. However, the Office Action confirms that Preissner et al. fails to specifically disclose that the PAI-1/vitronectin complex is a complex of active PAI-1 with vitronectin. The Office Action contends that, because the instant specification discloses that it is active PAI-1 that is bound to vitronectin, it is inherent that PAI-1 in complex with vitronectin is active. Further, the Office Action confirms that Preissner et al. does not specifically teach detecting PAI-1 in complex with the multimeric form of vitronectin. The Office Action states that the monoclonal anti-vitronectin antibody VN-P1C5 binds selectively to multimeric vitronectin.
- Wiman et al. teaches that functionally active PAI-1 in plasma is complexed with a binding protein identified as vitronectin. The Office Action confirms that Wiman et

al. does not address the issue of whether vitronectin bound to PAI-1 is monomeric or multimeric.

- DeClerck et al. teaches that PAI-1 exists in complex with vitronectin, and further characterizes the PAI-1-vitronectin complex, and demonstrates that the multimeric form of vitronectin binds to PAI-1.
- Harlow et al. teaches that immunoassay methods can be powerful, quick and easy methods for detection and quantification of antigens.

The Examiner contends, from all of these references, that it would have been obvious to one of ordinary skill in the art at the time of the invention to measure the amount of active PAI-1/multimeric vitronectin complex as a marker of disease in order to predict myocardial infarction. Further, The Examiner contends that one would have a reasonable expectation of success in measuring multimeric, rather than all forms of vitronectin complexed with PAI-1 because Preissner et al. teaches the monoclonal anti-Vn antibody VN-P1C5, which recognizes only dimeric (multimeric) but not monomeric or reduced vitronectin. The Office Action refers to page 1991, right column, first paragraph, and Figure 3 and legend as support of this assertion.

Applicants respectfully traverse. Applicants assert that the claimed invention would not have been obvious to one of ordinary skill in the art at the time this invention was made on the basis of the disclosures of the cited references, alone or in any combination.

Applicants respectfully point out that a determination under § 103 that an invention would have been obvious to someone of ordinary skill in the art is a conclusion of law based on fact. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1593, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 107 S.Ct. 2187. After the involved facts are determined, the decision maker must then make the legal determination of whether the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. *Id.* at 1596.

The United States Patent and Trademark Office (USPTO) has the initial burden under § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, the USPTO must satisfy three requirements. First, the prior art reference or combination of references *must teach or suggest all of the limitations of the claims*. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art"). The teachings must come from the prior art, not from applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Second, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some *suggestion or incentive that would have motivated* the skilled artisan to modify a reference or to combine references. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, the proposed modification or combination of the prior art must have a *reasonable expectation of success*, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

Furthermore, M.P.E.P. § 2143 states that under § 103, the cited reference or references must teach or suggest *all* the recitations of the claims, and there must be some *suggestion or motivation*, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.* M.P.E.P. §2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). As emphasized by the Court of Appeals for the Federal Circuit, to support combining references, evidence of a suggestion, teaching, or motivation to combine must be *clear and particular*, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). In another decision,

the Court of Appeals for the Federal Circuit has stated that, to support combining or modifying references, there must be particular evidence from the prior art as to the reason the skilled artisan, *with no knowledge of the claimed invention*, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

Applicants respectfully submit that Hamsten, Preissner et al., Declerck et al., Wiman et al., and Harlow et al., alone or in any combination, do not teach or suggest the methods of the present invention because none of these references teach or suggest that the amount of active PAI-1 in a sample can be determined by measuring the amount of PAI-1/multimeric vitronectin complex in that sample.

Further, one of skill in the art would not be motivated to carry out the methods of the present invention or have any reasonable expectation of success in measuring multimeric, rather than all forms of vitronectin, complexed with PAI-1, for at least the following reasons.

First, DeClerck et al. teaches that PAI-1 binds to both monomeric and oligomeric S protein (i.e., monomeric and multimeric vitronectin) (see page 15460, first column, second paragraph). Applicants thus submit that this reference actually *teaches away* from the use of a PAI-1/multimeric specific vitronectin complex alone to predict the amount of active PAI-1 in a sample.

Second, with regard to Preissner et al., the Office Action contends that because the instant specification discloses that it is active PAI-1 that is bound to vitronectin, it is inherent that PAI-1 in complex with vitronectin is active. Applicants respectfully submit that inherency cannot be used to support an obviousness objection.

Specifically, it is stated in § 2141.02 of the M.P.E.P., with a citation to *In re Rijckaert*, that "[o]bviousness cannot be predicated on what is not known at the time an invention was

made, even if the inherency of a certain feature is later established." 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). Thus, the use of the Preissner et al. reference for its allegedly inherent teachings as a necessary basis for this obviousness rejection renders the rejection improper and applicants request that it be withdrawn for at least this reason.

Applicants also note that none of the cited references, and certainly not Preissner et al., teach that active PAI-1 is bound to multimeric vitronectin. Further, applicants note that Preissner et al. teaches a method of measuring the amount of PAI-1 in complex with vitronectin in platelet releasates and platelet lysates. Applicants respectfully submit that, because the Office Action contends that platelet releasates and platelet lysates are not taught or supported by the present specification (see above), they further are not enough to maintain an obviousness objection. Applicants note that the invention as a whole must be found in the references cited in an obviousness rejection. Applicants are claiming an assay for biological fluids selected from whole blood, plasma and serum, and are no longer claiming platelet releasates and platelet lysates, further distinguishing this reference from the claimed invention.

In addition, applicants note that the Office Action states that the monoclonal anti-vitronectin antibody VN-P1C5 used in Preissner et al. binds selectively to multimeric vitronectin. However, this is contradictory to the statement in the Office Action that Preissner et al. does not specifically teach detecting PAI-1 in complex with the multimeric form of vitronectin, and is incorrect. Preissner et al. states that VN-P1C5 only identifies the intact form of vitronectin (see page 1991, first paragraph, second column, where Preissner et al. indicates that the antibody identifies the total 78Kd monomeric form, but not the 65 Kd band nor the 10 Kd piece). As seen in the non-reduced gels found in the figures in Preissner et al., the antibody identified a complex of less than 200Kd, and no trace of higher molecular weight forms. This complex would, by necessity, be of the monomeric form of vitronectin and not the multimeric form, because a complex containing the multimeric form would have a larger size. Thus, the very antibody cited in the Office Action further demonstrates the nonobviousness of this invention, and *teaches away*

from the use of a measure of active PAI-1 bound to multimeric vitronectin as a measure of total active PAI-1 in a sample.

Applicants respectfully submit that none of the prior art references cited, either alone or in combination, teach or suggest a method for determining active PAI-1 in a biological fluid by measuring the amount of active PAI-1/multimeric vitronectin complex in a sample. Further, as set forth above, none of these references provide the requisite motivation or expectation of success in carrying out the methods of this invention and therefore this invention would not have been obvious to one of ordinary skill in the art at the time it was made.

In addition, as stated previously, the claimed invention has significant distinguishing features as compared to the methods of the cited prior art, such features, on their own, rendering the claimed invention unobvious over the cited prior art. Namely, the amount of vitronectin bound to PAI-1 is known to be less than 0.1% of the total vitronectin in serum. Therefore, the methods described in the prior art would require binding an excess amount of antibody to all the vitronectin in the serum, meaning much larger amounts of antibody would be required as compared to the methods of the present invention. By measuring the amount of PAI-1/multimeric vitronectin complex instead of measuring all of the vitronectin in the sample, one reduces costs and eliminates steps. This reduction of costs and steps is achieved by the methods claimed herein.

The arguments presented above pertain to all of claims 1-11 and 23-24, none of which would have been obvious in view of the cited references, thereby overcoming this rejection and applicants respectfully its withdrawal.

B. The Office Action states that claims 12-13 are rejected under 35 USC 103(a) as allegedly being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al., as applied to claim 1 above, and further in view of Forrest et al.

specifically, the Office Action states that Forrest et al. teaches a sandwich-type immunoassay using two antibody reagents.

As explained above, the claimed invention is not obvious over Hamsten in view of Preissner et al., Declerk et al., Wiman et al., and Harlow et al. The elements and suggestions missing from these references are not provided by the addition of these general disclosures of Forrest et al. Therefore it is respectfully requested that this rejection be withdrawn.

C. The Office Action states that claims 16-18 are rejected under 35 USC 103(a) as allegedly being unpatentable over Hamsten in view of Preissner et al., Declerck et al, Wiman et al., and Harlow et al., in further view of Ehrlich et al. Specifically, the Office Action states that Ehrlich et al. teaches that in sandwich immunoassays, the labeled antibody may be labeled with a directly or indirectly detectable label, and that either is suitable so long as it allows for the detection of the antibody when bound to a solid support.

As explained above, the claimed invention is not obvious over Hamsten in view of Preissner et al., Declerk et al., Wiman et al., and Harlow et al. The elements and suggestions missing from these references are not provided by the inclusion of the these general disclosures of Ehrlich et al. Therefore it is believed that this rejection has been overcome and its withdrawal is respectfully requested.

D. The Office Action has stated that claims 19-22 are rejected under 35 USC 103(a) as being unpatentable over Hamsten in view of Preissner et al., Declerck et al., Wiman et al., and Harlow et al., further in view of Valenzuela et al. Specifically, the Office Action states that Valenzuela et al. teaches that antibody labels can include fluorophores such as rhodamine, and luminescent materials such as acridinium ester compounds.

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As explained above, the claimed invention is not obvious over Hamsten in view of Preissner et al., Declerk et al., Wiman et al., and Harlow et al. The elements and suggestions missing from these references are not provided by the inclusion of these general disclosures of Valenzuela et al. Therefore, this rejection is believed to be overcome and its withdrawal is respectfully requested.

Having addressed all of the issues raised in the Office Action, applicants believe that the present claims are in condition for allowance, which action is respectfully requested. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of this application to issuance.

The Commissioner is authorized to charge Deposit Account No. 50-0220 in the amount of $1310.00 ($510.00 as the fee for a three-month extension of time and $800.00 additional claim fees for a small entity). This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION UNDER 37 C.F. R. § 1.8

Date of Deposit: February 26, 2007

I hereby certify that this correspondence is being submitted to the United States Patent and Trademark Office under 37 CFR 1.8 via facsimile transmission to 571-273-8300 on the date indicated above and is addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Tracy Wallace